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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/551,603	01/20/2006	Thomas C. Schulz	18377-0067	8027

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EXAMINER	
SAJJADI, FEREYDOUN GHOTB	
ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/551,603	SCHULZ ET AL.	
	Examiner	Art Unit	
	FEREYDOUN G. SAJJADI	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,9,31 and 75-81* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,9,31 and 75-81* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Request for Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission and amendment filed on June 9, 2008, that includes a response to the advisory action dated May 20, 2008, has been entered. Claims 1, 2, 4-9, 31 and 75-81 are pending in the application. Claims 1 and 31 have been amended. Claims 10-18 were cancelled and claims 75-81 newly added.

Claims 1, 2, 4-9, 31 and 75-81 are currently under examination.

Objection to the Specification-Title

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

New Claim Rejections - 35 USC § 112- Second Paragraph

Claims 1, 2, 4-9, 31 and 75-81are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 31 are unclear. The claims recite human aneuploid embryonic stem cell cultures, wherein a majority of cells have an abnormal karyotype and wherein the cells of the culture do not express SSEA1, but express SSEA3, SSEA4, Oct4, Tra-1-60, Tra-1-80 and nestin. However, it is not clear whether the cells expressing said markers are the majority of cells with the abnormal karyotype, or the remaining cells in the culture. As it is not clear which cell types are actually being claimed, the metes and bounds of "the cells of the culture" remains undefined.

Claims 2 and 4-9 depend from base claim 1; and claims 75-81 depend from base claim 31; and are therefore included in the rejection.

New Claim Rejections - 35 USC § 112- New Matter

Claims 1, 2, 4-9, 31 and 75-81 are newly rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art (hereafter the Artisan), that the inventor(s), at the time the application was filed, had possession of the claimed invention. 37 CFR §1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application".

Base claim 1 and 31 recite human aneuploid embryonic stem cell cultures, wherein a majority of cells have an abnormal karyotype and wherein the cells of the culture do not express SSEA1, but express SSEA3, SSEA4, Oct4, Tra-1-60, Tra-1-80 and nestin substantially uniformly.

Applicants state that no new matter has been presented in the amendment. Such is not found persuasive, because the specification fails to disclose either explicitly or implicitly, the characterization of any aneuploid embryonic stem cells cultured to express the combination of cell surface markers, either with a specification combination of chromosomal abnormalities, or as a majority of cells, as claimed. Example 11 of the instant specification discloses that sorted HESCs were positive for the combination of SSEA3, SSEA4, Oct4, Tra-1-60, Tra-1-80 and nestin; and negative for SSEA1 (paragraph [0176], p. 65). Example 19 describes various abnormal karyotypes for hESC BG01-derived cell lines, that include trisomies 1, 7, 8, 12, 14 and 17 and other mixed karyotypes (paragraph [0212], p. 78). However, the instant specification is silent on which specific autosomal abnormality corresponds to the specific combination of markers claimed. The specification is therefore silent on establishing a clear nexus between a particular karyotypic aneuploidy and the expression pattern of the cell surface markers claimed.

Thus, at the time the application was filed, an Artisan of skill would not recognize from the disclosure that Applicant was in possession of any of numerous human aneuploid stem cells

that regardless of their karyotypic abnormality, express SSEA3, SSEA4, Oct4, Tra-1-60, Tra-1-80 and nestin, either as an individual cell line or as a majority of cells in a mixed stem cell culture, as claimed.

MPEP 2163.06 notes: "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure".

This is a new matter rejection.

Response and New Claim Rejections - 35 USC § 112-Scope of Enablement

Claim 1, 2, 4-9 and 31 stand rejected under 35 U.S.C. 112, first paragraph, in modified form, as failing to comply with the enablement requirement. The rejection set forth on pp. 4-7 of the office action dated July 25, 2007, pp. 3-4 of the final office action dated Feb. 7, 2008, and the advisory action dated May 20, 2008, is maintained in modified form for claims 1, 2, 4-9 and 31 and further applied to newly added claims 75-81 for reasons of record.

The lack of enablement previously indicated is hereby modified to set forth an enabled scope for the instant claims, in view of the evidence supplied by Applicants. Accordingly, the claims are enabled for the human aneuploid embryonic stem cell line BG01V derived from human ES cell line BG01, deposited as ATCC No. SCRC-2002.

Applicants state that they have entered into a commercialization licensing agreement with Invitrogen, for the sale of one of Applicants' exemplary aneuploid embryonic stern cell lines,

BG01v (Exhibit A), and as a research tool and to create cDNA libraries (Exhibit B). Applicants have additionally provided Exhibits C-F as exemplary for the utility of the BGO1V cell line. Applicants argue that the particular chromosomal abnormality present in any of the aneuploid embryonic stem cell lines is not relevant to the primary utilities outlined above, and thus, any suitable aneuploid cell cultures made by the present invention would be enabled for such research. The invention provides aneuploid embryonic stem cell lines that have been selected through the protease passaging process for a preferred, though "abnormal," chromosomal advantage as evidenced by their ability to reproduce more effectively than the karyotypically "normal" cells, Therefore, an advantage of the claimed cultures is their relative experimental stability as compared to karyotypically normal cells, which are generally more difficult to culture. Applicants additionally refer to the Table on p. 78 of the specification, that disclose various karyotypic abnormalities identified from passaging the BG01 cell line, further arguing that the BG01 cell line is not the only cell line enabled by the current invention, and that the claims are directed generically to methods and cell cultures of human aneuploid embryonic stem cells.

Applicants' arguments have fully considered but are found persuasive only in part. As an initial matter, it should be noted that the instant claims are product claims, and not method claims. Further, the instant claims are further directed to any human aneuploid embryonic stem cell having the particular cell surface marker profile of $SSEA1^-$, $SSEA3^+$, $SSEA4^+$, $Oct\text{-}4^+$, $Tra\text{-}1\text{-}80^+/81^+$ and $nestin^+$. However, as previously indicated, Example 11 of the instant specification discloses that sorted HESCs were positive for the combination of SSEA3, SSEA4, Oct4, Tra-1-60, Tra-1-80 and nestin; and negative for SSEA1 (paragraph [0176], p. 65). Example 19 describes various abnormal karyotypes for hESC BG01-derived cell lines, that include trisomies 1, 7, 8, 12, 14 and 17 and other mixed karyotypes (paragraph [0212], p. 78). However, the instant specification is silent on which specific autosomal abnormality corresponds to the specific combination of markers claimed. The specification is therefore silent on establishing a clear nexus between a particular karyotypic aneuploidy and the expression pattern of the cell surface markers claimed. Moreover, the instant specification refers to Tra-1-80 as a defining marker of the instantly claimed cells throughout, but Example 11, teaches that the sorted hESCs were Tra-

1-81$^+$. Therefore, a person of skill in the art would not be able to resolve the inconsistency, without further undue experimentation.

The post-filing evidence provided Applicants demonstrates the use of the BG01V cell line in various research applications, but additionally presents conflicting results with respect to this cell line. For example, Example B, from Invitrogen characterizes the cell line as having an abnormal karyotype 48XY/12+/17+. By contrast, Exhibit F, Zeng et al. characterized the cell line's karyotype as 49XXY, 12+,17+. The Exhibits additionally fail to ascribe the instantly claimed cell surface marker profile to the BG01V cell line. The instant claims encompass numerous karyotypically distinct cells derived from any of numerous human ES cell sources that all exhibit a specific cell surface marker signature or profile. Such is inconsistent with the teachings of both the instant specification and those of the prior art. Applicants' assertion that any abnormal ES cell having any of numerous possible aneuploidies would at once be SSEA1$^-$, SSEA3$^+$, SSEA4$^+$, Oct-4$^+$, Tra-1-80$^+$/81$^+$ and nestin$^+$, and exhibit a phenotype identical to that of BG01V to allow a similar use, is unsubstantiated and would require further undue experimentation to elucidate.

Therefore, the rejection of claims 1, 2, 4-9 and 31 is maintained in modified form, and further applied to new claims 75-81 for reasons of record and the foregoing discussion.

New Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 2, 4-9, 31 and 75-81 are newly rejected under 35 U.S.C. 102(a) as being anticipated by Draper et al. (Nature Biotech. 22(1):53-54; published online Dec. 7, 2003), as evidenced by Mitalipova et al. (U.S. Patent Publication No.: 2005/0037488; effective filing date Aug. 6, 2001) and Nakayama et al. (U.S. Patent Publication No.: 2005/0221479; effective filing date June 23, 2003).

As previously of record, Example 19 of the instant specification discloses that the cells showed abnormal karyotypes only following 32 or more passages, and included various autosomal trisomies. No such disclosure is present in the provisional Application 60/459,090. Thus, an artisan of skill would not be apprised of cellular aneuploidy as a result of specific passage number and conditions, or the nature of said aneuploidy, and would therefore not recognize that Applicants had possession of cells carrying specific karyotype abnormalities that included autosomal trisomies of chromosomes 1, 7, 8, 12, 14 and 17, as instantly claimed, that further do not express SSEA1, but express SSEA3, SSEA4, Oct4, Tra-1-60, Tra-1-80 and nestin, from the disclosure of the '090 Application. Therefore, the effective filing date of the instant claims is the filing date of PCT/US04/10121, filed 3/31/2004.

The rejection is applicable to the extent that the instant claims are enabled for a human aneuploid embryonic stem cell culture, comprising a cell with an abnormal karyotype that is either trisomy 12 or 17, or both.

The instant claims encompass cells expressing nestin, that appear to be at least partially differentiated along the neuronal path in embryoid bodies. Base claim 31 is drawn to a human aneuploid embryonic stem cell produced by antibody selection and maintenance in culture; and is thus a product by process claim.

MPEP 2112.01 states: "Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established. *In re Best,* 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977)." MPEP 2113 further states: "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985).

Draper et al. teach the recurrent gain of chromosomes 17 and 12 in cultured human embryonic stem cells, wherein the cells retained an undifferentiated phenotype, were surface

positive for SSEA3, Tra-1-60 and Oct4, and retained an ability to differentiate in culture (Title and first column, p. 53). With respect to the surface markers SSEA1$^-$, SSEA4$^+$, Tra-1-80$^+$/81$^+$ and nestin$^+$, it should be noted that these limitations would be pertinent should evidence be provided that the instantly claimed stem cells are structurally distinct from those disclosed by Draper et al. While Draper et al. did not test their aneuploid cells for the SSEA1$^-$, SSEA4$^+$, Tra-1-80$^+$ and nestin surface marker, such would be an inherent property of their stem cells, and the existence of these cell surface marker was known in the prior art, as evidenced by Mitalipova et al. who teach human ES cells staining positively for OCT-4 (FIG. 4A), Tra-1-60 (FIG. 4C), SSEA-3 (FIG. 4E), and SSEA4, (FIG. 4H); and negative for SSEA1 (FIG. 4J) cell surface markers (paragraph [0036]); and that known markers of pluripotent ES cells include stage specific embryonic antigen TRA-1-81 (paragraph [0090]). The neural marker nestin is taught by Nakayama et al. in differentiating stem cells (paragraph [0217]).

"When the structure recited in the reference is substantially identical to that of the claims, claimed properties or functions are presumed to be inherent." See MPEP 2112.01 or *In re Best*, 195 USPQ 430, 433 (CCPA 1997). As stated in MPEP 2112: The express, implicit, and inherent disclosures of a prior art reference may be relied upon in the rejection of claims under 35 U.S.C. 102 or 103. "The inherent teaching of a prior art reference, a question of fact, arises both in the context of anticipation and obviousness." *In re Napier*, 55 F.3d 610, 613, 34 USPQ2d 1782, 1784 (Fed. Cir.1995) (affirmed a 35 U.S.C. 103 rejection based in part on inherent disclosure in one of the references). See also *In re Grasselli*, 713 F.2d 731, 739, 218 USPQ 769, 775 (Fed. Cir. 1983).

Moreover, "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977).

When the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to

prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See *In re Ludtke* 441 F.2d 660, 169 USPQ 563 (CCPA 1971). Whether the rejection is based on "inherency" under 35 USC 102; or "*prima facie* obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. *In re Best, Bolton, and Shaw*, 195 USPQ 430, 433 (CCPA 1977) citing *In re Brown*, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972).

The examiner further maintains that the office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of factual evidence to the contrary, the burden is upon the applicant to prove that the claimed products are **functionally different** than those taught by the prior art and to establish patentable differences. See *Ex parte Phillips,* 28 USPQ 1302, 1303 (BPAI 1993), *In re Best,* 562, F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray,* 10 USPQ2d 1922, 1923 (BPAI 1989). The claiming of a new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977); *In re Spada,* 15 USPQ2d 1655, Federal Circuit, 1990. See also MPEP § 2112.01 with regard to inherency and product-by-process claims.

Therefore by teaching all the limitations of the claims Draper et al. anticipate the instant invention as claimed.

Conclusion

Claims 1, 2, 4-9, 31 and 75-81 are not allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to FEREYDOUN G. SAJJADI whose telephone number is (571)272-3311. The examiner can normally be reached on 6:30 AM-3:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Fereydoun G Sajjadi/
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